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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/779,447
Filing Date: February 09, 2001
Appellant(s): BANERJEE ET AL.

Heath W. Hoglund
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/26/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

Claims 9, 14 and 18 have been amended subsequent to the final rejection.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 9, 14 and 18 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Banerjee et al., Indian J. Biochem. and Biophysics, vol. 30(6), pp. 389-94.

Tiganis et al., Exp. Cell Research, vol. 198, pp. 191-200, 1992.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 14 and 18 are rejected under 35 U.S.C. 103 as being unpatentable over Banerjee et al., *Indian J. Biochem. and Biophysics*, vol. 30(6), pp. 389-94 and Tiganis et al., *Exp. Cell Research*, vol. 198, pp. 191-200 (1992).

Claims 9, 14 and 18 are drawn to a method for inhibiting angiogenesis comprising administering a pyrimidine nucleoside, wherein the nucleoside comprises N-acetylated glucosamine or comprises tunicamycin and functional derivatives thereof administered with daily and weekly dosages.

Banerjee teaches that angiogenesis comprises (1)endothelial cell proliferation and (2) differentiation into blood capillaries. Banerjee teaches the use of a pyrimidine nucleoside as an antiangiogenic agent as it teaches that the angiogenic process of capillary endothelial cell proliferation is linked to the synthesis of N-linked oligosaccharide chains which is inhibited by the pyrimidine nucleoside tunicamycin (which contains a linked glucosamine). Tiganis et al., further supports the recognition in the prior art of the inhibition of N-glycosylation

by tunicamycin and the disruption of vascular proliferation or angiogenesis. Tiganis teaches that the inhibition of glycoproteins by tunicamycin impairs the cell adhesion and the functional properties of the endothelial lining of the blood vessels. Thus one of skill in the art would have a reasonable expectation of success that if Tunicamycin is a potent inhibitor of N-glycosylation and that this inhibition disrupts component (1) of angiogenesis, there is clearly a reasonable expectation of success in the use of tunicamycin as an agent which would inhibit angiogenesis.

Banerjee does not specifically mention the functional derivatives of tunicamycin nor the timetable administration to a patient; however, characteristics normally possessed by members of a homologous series are principally the same, chemists would in general know what to expect in adjacent members of homologs of a known compound. The test of patentability of a compound that is a homologue of a prior art compound is whether the claimed compound possesses beneficial characteristics which are unexpected and unobvious. One of skill in the art would have a reasonable expectation of success in the use of homologs of tunicamycin as angiogenic compounds given the efficacy of the parent compound. There is not data in the prior art nor the specification that presents some property of these homologs apart from that of the parent compound, chiefly the inhibition of angiogenesis. One of skill in the art would also have a reasonable expectation of success that a compound which inhibits angiogenesis would be beneficial in various disease states which may be

disrupted by or thrive on the process of angiogenesis. Applicant's claims regarding the administration timetable of the know compound is not patentable given that one of skill in the art practicing the administration of any medical compound determines the optimum dosage for each patient, based on a variety of physical and metabolic factors.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use a pyrimidine nucleoside such as tunicamycin to inhibit angiogenesis.

A person of ordinary skill in the art would have been motivated to use a pyrimidine nucleoside such as tunicamycin given the prior art's recognition of tunicamycin as an inhibitor of the pathway leading to the angiogenic process of capillary endothelial cell proliferation.

(11) Response to Argument

Applicant's primary argument is that the prior art discloses the *in vitro* application of Tunicamycin to endothelial cells and angiogenesis, while the invention as claimed targets *in vivo*. Applicant should note that the instant disclosure is solely based on *in vitro* data (emphasis added). Applicant has not presented any data demonstrating an *in vivo* use in the instant disclosure and the suggestion of a dosage does not demonstrate an *in vivo* use. While a demonstration of *in vivo* use in a disclosure is not absolutely required to support claims thereto, it is clear that applicant's disclosure uses *in vitro* data to support the inhibition of angiogenesis while contending that the same use of *in vitro* data

in the prior art of is not correlative. The recitation of specific dosage intervals represents a protocol for administering Tunicamycin to achieve the same effect already recognized in the prior wherein the claims to specific dosages and time periods are based on *in vitro* data that was previously presented in the prior art.

One of skill in the art need not be certain of the efficacy of a compound to constitute a reasonable motivation to use the compound for an asserted utility. Using the rationale set forth in *In re Brana*, 51 F.3d 1560, the test as to whether an *in vitro* model provides sufficient correlation to an *in vivo* model is whether the "[*in vitro*] model represents a specific disease against which the claimed compounds are alleged to be effective", *Brana*, 1565. As such, the *in vitro* data presented by Banerjee and Tiganis that use of the compound Tunicamycin inhibits angiogenesis provides a reasonable correlation and motivation to use the compound *in vivo*.

As cited supra, Banerjee teaches that angiogenesis comprises (1) endothelial cell proliferation and (2) differentiation into blood capillaries. Banerjee teaches the use of a pyrimidine nucleoside as an antiangiogenic agent as it teaches that the angiogenic process of capillary endothelial cell proliferation is linked to the synthesis of N-linked oligosaccharide chains which is inhibited by the pyrimidine nucleoside tunicamycin (which contains a linked glucosamine). Banerjee teaches that protein N-glycosylation and angiogenesis are indeed interlinked (p.293, ¶ 3); moreover, that Tunicamycin inhibited N-glycosylation in control cells by 64% and those treated with isoproterenol by 70% (p. 392, col.1-col.2). Thus Banerjee has

recognized that Tunicamycin is a potent N-glycosylation inhibitor, as such given the teachings by Banerjee that angiogenesis is linked to N-glycosylation, one of skill in the art would have a reasonable expectation of success in the use of Tunicamycin to inhibit angiogenesis.

Applicant also asserts that Tiganis et al. (Tiganis) teaches away from the *in vivo* use of Tunicamycin because of the adverse side effect of tunicamycin, wherein applicant cites p. 199 of Tiganis. Prior to p. 199, Tiganis cites on p. 198, col. 2, paragraph 3 "Tunicamycin inhibited the growth and was cytotoxic for dividing endothelial cells but did not inhibit the growth and was not cytotoxic for confluent cells". The reference to adverse side effects was when Tunicamycin is used at an art recognized toxic level (p. 199 – co. 2, paragraph 1):

"Since a feature of tunicamycin toxicity in animals is impaired permeability of brain microvessels an important question whether tunicamycin has a direct effect on microvessels *in vivo* and if so whether glycoprotein components on the tight junctions are specifically altered".

It is clear from this citation that Tiganis was not wholly inferring that use of Tunicamycin in any capacity results in brain damage but merely reflecting on evidence seen in the prior art when Tunicamycin is administered at a toxic level; moreover, since the prior art has recognized the levels at which tunicamycin toxicity occurs, one of skill in the art would know what dosage levels would be inappropriate.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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January 7, 2005

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